Ultrasound Obstet Gynecol 2021; **58**: 450–456
Published online 9 August 2021 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.23729

Short-term outcome of pregnant women vaccinated with BNT162b2 mRNA COVID-19 vaccine

S. BOOKSTEIN PERETZ[1,2#], N. REGEV[1#], L. NOVICK[1], M. NACHSHOL[1], E. GOFFER[3], A. BEN-DAVID[1,2], K. ASRAF[4], R. DOOLMAN[4], E. GAL LEVIN[2,5], G. REGEV YOCHAY[2,5] and Y. YINON[1,2]

[1]*Department of Obstetrics and Gynecology, Sheba Medical Center, Tel Hashomer, Israel;* [2]*Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel;* [3]*Institute for Medical Engineering and Science, Massachusetts Institute of Technology, Cambridge, MA, USA;* [4]*Automated Mega Laboratory, Sheba Medical Center, Tel Hashomer, Israel;* [5]*Infection Prevention & Control Unit, Sheba Medical Center, Tel Hashomer, Israel*

KEYWORDS: COVID-19; obstetric outcome; pregnancy; SARS-CoV-2 antibodies; vaccine

CONTRIBUTION

What are the novel findings of this work?
The BNT162b2 mRNA coronavirus disease 2019 (COVID-19) vaccine is safe for use in pregnant women in view of its adverse-effect profile and associated favorable short-term obstetric and neonatal outcomes. The vaccine is effective in inducing humoral immunity in pregnant women, although severe acute respiratory syndrome coronavirus 2 immunoglobulin G levels were lower when compared with those in non-pregnant vaccinated women.

What are the clinical implications of this work?
The findings of this study show that COVID-19 vaccination of pregnant women with the BNT162b2 mRNA vaccine seems to be safe and effective. Recommending COVID-19 vaccination of pregnant women should therefore be strongly considered in view of the maternal morbidity associated with COVID-19 in pregnancy.

ABSTRACT

Objectives *To determine the immunogenicity and reactogenicity of the Pfizer/BioNTech BNT162b2 mRNA coronavirus disease 2019 (COVID-19) vaccine among pregnant women compared with non-pregnant women, and to evaluate obstetric outcome following vaccination.*

Methods *This was an observational case–control study of pregnant women who were vaccinated with a two-dose regimen of the BNT162b2 vaccine during gestation between January and February 2021 (study group) and age-matched non-pregnant women who received the vaccine during the same time period (control group). Participants received a digital questionnaire 1–4 weeks after the second dose and were asked to provide information regarding demographics, medication, medical history, history of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, timing of COVID-19 vaccine doses and side effects after each vaccine dose. A second digital questionnaire, regarding current pregnancy and delivery outcomes, was sent to patients in the study group after the calculated due date. All recruited women were offered a serology blood test for SARS-CoV-2 immunoglobulin G (IgG) following the second vaccination dose and SARS-CoV-2 IgG levels were compared between the two groups.*

Results *Of 539 pregnant women who were recruited after completion of the two-dose regimen of the vaccine, 390 returned the digital questionnaire and were included in the study group and compared to 260 age-matched non-pregnant vaccinated women. The rates of rash, fever and severe fatigue following vaccination among pregnant women were comparable to those in non-pregnant women. Myalgia, arthralgia and headache were significantly less common among pregnant women after each dose, local pain or swelling and axillary lymphadenopathy were significantly less common among pregnant women after the first and second doses, respectively, while paresthesia was significantly more common among the pregnant population after the second dose. Among pregnant women, there were no significant differences in the rates of side effects according to whether the vaccine was administered during the first, second or third trimester of pregnancy, except for local pain/swelling, which was significantly less common after*

Correspondence to: Prof. Y. Yinon, Department of Obstetrics and Gynecology, Sheba Medical Center, Tel Hashomer, 52621, Israel (e-mail: yoav.yinon27@gmail.com)

#S.B.P. and N.R. contributed equally to this study.

Accepted: 28 June 2021

the first dose when administered during the third trimester, and uterine contractions, which were significantly more common after the second dose when administered during the third trimester. The rates of obstetric complications, including uterine contractions (1.3% after the first dose and 6.4% after the second dose), vaginal bleeding (0.3% after the first dose and 1.5% after the second dose) and prelabor rupture of membranes (0% after the first dose and 0.8% after the second dose), were very low following vaccination. All serum samples in both groups were positive for SARS-CoV-2 IgG. However, pregnant women had significantly lower serum SARS-CoV-2 IgG levels compared to non-pregnant women (signal-to-cut-off ratio, 27.03 vs *34.35, respectively;* $P < 0.001$*). Among the 57 pregnant women who delivered during the study period and who completed the second questionnaire, median gestational age at delivery was 39.5 (interquartile range, 38.7–40.0) weeks, with no cases of preterm birth < 37 weeks, no cases of fetal or neonatal death and two (3.5%) cases of admission to the neonatal intensive care unit for respiratory support.*

Conclusions *The adverse-effect profile and short-term obstetric and neonatal outcomes among pregnant women who were vaccinated with the BNT162b2 vaccine at any stage of pregnancy do not indicate any safety concerns. The vaccine is effective in generating a humoral immune response in pregnant women, although SARS-CoV-2 IgG levels were lower than those observed in non-pregnant vaccinated women.* © *2021 International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

The novel coronavirus, identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), has led to substantial morbidity and mortality globally[1]. Accumulating evidence indicates that pregnant women are more likely to experience COVID-19-related complications compared with non-pregnant women, including need for invasive ventilation, admission to an intensive care unit and death[2–10].

The novel BNT162b2 (Pfizer/BioNTech) mRNA vaccine against COVID-19 has been shown recently to be effective both in a randomized trial and in a nationwide mass vaccination setting[11–14]. However, pregnant women were excluded from all initial clinical trials reviewing the BNT162b2 vaccine[11–14], as well as from trials testing other vaccines approved by the Food and Drug Administration (FDA). The first clinical trial of the Pfizer/BioNTech vaccine in pregnant women began in February 2021 and the results have yet to be published.

The BNT162b2 vaccine is based on a novel approach that utilizes mRNA to synthesize the spike protein of SARS-CoV-2, which is recognized by the immune system[15,16]. Since mRNA vaccines have not previously been used in pregnant women prior to the COVID-19 pandemic, data on their efficacy, effectiveness and safety in pregnancy are limited, and it remains unclear whether this vaccine will drive immunity in pregnant women and whether it may affect pregnancy outcome[17]. A recent study which examined COVID-19-vaccine-induced antibody titers in pregnant *vs* non-pregnant women showed no significant difference between the groups, and antibody titers of vaccinated women were significantly higher than those induced by SARS-CoV-2 infection during pregnancy[18]. Another study demonstrated a robust maternal humoral response that was transferred effectively to the fetus, suggesting another role of vaccination during pregnancy[19].

Crucial data for decision-making and counseling regarding COVID-19 vaccination in pregnancy are still limited and, thus, most medical societies and agencies advise that a vaccine should be offered to pregnant women after discussing the risks and benefits and the lack of safety data, with preferential administration for those at highest risk of severe infection[20–22].

We report herein on the vaccine-induced immunity and adverse events associated with the BNT162b2 vaccine among pregnant women compared with non-pregnant women.

SUBJECTS AND METHODS

Study design and participants

This was an observational case–control study of pregnant women who were vaccinated using a two-dose regimen of the BNT162b2 (Pfizer/BioNTech) vaccine at 2–40 weeks of gestation, between January and February 2021, recruited via social media publications (study group). Pregnant women who gave birth or had an abortion before the second dose of vaccine were excluded. The study group was matched 1.5:1 by age to a control group of non-pregnant female patients who received a two-dose regimen of the BNT162b2 (Pfizer/BioNTech) vaccine at Sheba Medical Center, Tel Hashomer, Israel, during the same time period. The control group was recruited by the Infection Prevention & Control Unit of Sheba Medical Center, as part of a population cohort study.

Participants in both groups received a digital questionnaire 1–4 weeks after the second dose and were asked to provide information regarding demographics, medication, medical history, history of SARS-CoV-2 infection, timing of COVID-19 vaccine doses and side effects after each vaccine dose. The side effects that participants were asked about were redness/swelling/pain around the area of injection, rash, fever (> 38°C), severe fatigue, arthralgia, myalgia, axillary lymphadenopathy, paresthesia and headache. Pregnant women in the study group were also questioned about obstetric symptoms following the vaccine, including uterine contractions, vaginal bleeding and prelabor rupture of membranes (PROM) during the first 7 days after each dose. A second digital questionnaire, regarding current pregnancy and delivery outcomes, was sent to patients in the study group after their calculated due date.

All patients were offered a serology blood test for SARS-CoV-2 immunoglobulin G (IgG) following the

second vaccination dose. For this analysis, patients from the study group were matched 1:1 to the control group for time since the second dose of the vaccine, age and body mass index (BMI).

The study was approved by the Sheba Medical Center institutional review board (8042-21). All participants provided informed consent, either telephonically for the digital questionnaire or in writing for participants who were tested for reactive SARS-CoV-2 antibodies.

Sample collection and processing and antibody quantification

A single blood sample was collected 2 weeks to 2 months after the second dose of the vaccine. Blood was collected by venipuncture into a serum separator tube. All samples were centrifuged at 4000 *g* for 4 min at room temperature.

The samples were tested for SARS-CoV-2 receptor-binding domain (RBD) IgG using the commercial automatic Access SARS-CoV-2 IgG immunoassay (Beckman Coulter, CA, USA), which is a two-step enzyme immunoassay, according to manufacturer's instructions. Briefly, the sample was added to a reaction vessel with buffer and paramagnetic particles coated with recombinant SARS-CoV-2 protein specific for the RBD of the S1 protein. After incubation in the reaction vessel, materials bound to the solid phase were held in a magnetic field, while unbound materials were washed away. A monoclonal anti-human IgG alkaline phosphatase conjugate was added, which binds to the IgG antibodies captured on the particles. A second separation and wash step were performed to remove unbound conjugate. A chemiluminescent substrate was added to the vessel and light generated by the reaction was measured using a luminometer. The light production was compared to the cut-off value defined during calibration of the instrument.

Test results were determined automatically by the system software. Detection of analyte in the sample was determined from the measured light production by means of the stored calibration data. SARS-CoV-2 IgG titer signal-to-cut-off (S/CO) ratios < 0.8 were reported as non-reactive, those ≥ 0.8 to < 1.0 were reported as equivocal and those ≥ 1.0 were reported as reactive.

Statistical analysis

Normally distributed continuous data were described using mean ± SD, while non-normally distributed data were described using median and interquartile range (IQR). Univariate analyses were performed using the Student's *t*-test for normally distributed continuous variables and the Mann–Whitney *U*-test for non-normally distributed continuous variables. Chi-square test, or Fisher's exact test for small cell sizes, was used for categorical variables. Spearman's correlation was used to evaluate the association between gestational age at the time of the second vaccine and serum levels of SARS-CoV-2 IgG. One-way ANOVA was used to evaluate the association between trimester at the time of the second vaccine and serum SARS-CoV-2 IgG levels. Significance was accepted at $P \leq 0.05$. All analyses were conducted using SPSS 24 (SPSS Inc., Chicago, IL, USA).

RESULTS

Of 539 pregnant women who were recruited after completion of the two-dose regimen of the vaccine, 390 returned the digital questionnaire and were included in the study group and matched by age to a control group of 260 non-pregnant vaccinated women (Figure 1). Baseline characteristics of the study and control groups are shown in Table 1. The groups were comparable with respect to BMI and underlying medical conditions.

Reactogenicity

The incidence of adverse events following vaccination in the study and control groups is shown in Table 2. Myalgia, arthralgia and headache were significantly less common among pregnant women compared with in the control group following both the first and second doses of the vaccine, local pain or swelling was significantly less common in pregnant women only after the first dose and axillary lymphadenopathy was significantly less common

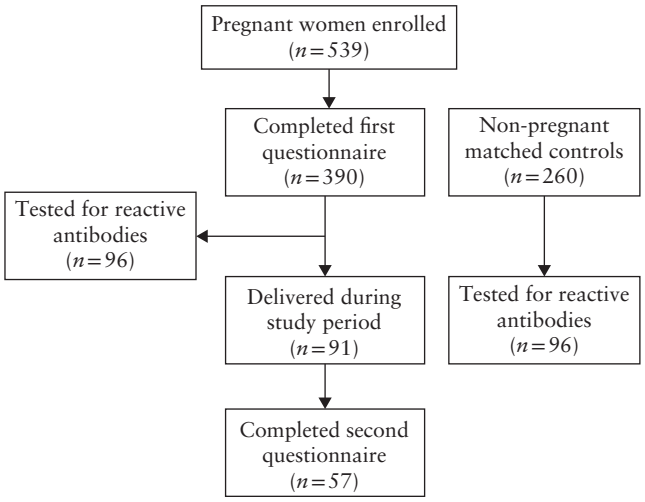

Figure 1 Flowchart showing enrolment of pregnant and non-pregnant women who received two doses of the BNT162b2 vaccine.

Table 1 Baseline characteristics of 390 pregnant and 260 non-pregnant women who received two doses of BNT162b2 vaccine

Characteristic	*Pregnant* (n = *390*)	*Non-pregnant* (n = *260*)	P
Age (years)	32.5 ± 3.7	32.4 ± 3.7	0.65
BMI (kg/m^2)	24.4 ± 5.2	23.8 ± 5.4	0.18
Chronic hypertension	2 (0.5)	2 (0.8)	0.69
Diabetes	13 (3.3)	4 (1.5)	0.15
Chronic heart disease	3 (0.8)	0 (0)	0.15
Chronic lung disease	21 (5.4)	5 (1.9)	0.5

Data are given as mean ± SD or *n* (%). BMI, body mass index.

in pregnant women only after the second dose. In contrast, paresthesia was more common among pregnant women compared with in the control group after the second dose. Other adverse events, including rash, fever and severe fatigue, did not differ between the two groups. Of note, fever > 38°C was experienced by 1.5% of pregnant women after the first dose and by 9% after the second dose of the vaccine, but only 0.8% of pregnant women had fever of 39°C or above following vaccination, all of whom were affected after the second dose. Moreover, the incidence of obstetric complications following vaccination was extremely low; uterine contractions occurred in five (1.3%) patients after the first dose and in 25 (6.4%) patients after the second dose of the vaccine. However, in 15 (60%) of the 25 patients who experienced contractions following the second dose, the contractions occurred after 34 weeks of gestation, and in none of the cases did the contractions result in preterm birth. In addition, vaginal bleeding was reported in only one (0.3%) pregnant woman after the first dose and in six (1.5%) pregnant women after the second dose of the vaccine. There were no cases of PROM during the first 7 days after the first dose of the vaccine, while three (0.8%) patients experienced PROM after the second dose at 36 + 3, 36 + 4 and 37 + 1 weeks of gestation.

A subanalysis of adverse events in pregnancy according to the trimester in which the first and second doses of the vaccine were administered is shown in Table 3. Seventy-six participants received the first dose of the vaccine during the first trimester of pregnancy, 193 during the second trimester and 121 during the third trimester. There were no significant differences in the rates of side effects according to whether patients were vaccinated in the first, second or third trimester, except for local pain/swelling, which was significantly less common after the first dose when administered during the third trimester, and uterine contractions, which were significantly more common after the second dose when administered during the third trimester.

Immunogenicity

Of the 390 included pregnant patients, 96 were tested for SARS-CoV-2 IgG 2 weeks to 2 months following the second vaccine dose. There was no difference in

Table 2 Adverse events after the first and second doses of BNT162b2 vaccine in 390 pregnant and 260 non-pregnant women

	First dose			*Second dose*		
Adverse event	*Pregnant (n = 390)*	*Non-pregnant (n = 260)*	P	*Pregnant (n = 390)*	*Non-pregnant (n = 260)*	P
Local pain/swelling	358 (91.8)	250 (96.2)	0.02	360 (92.3)	235 (90.4)	0.38
Rash	3 (0.8)	2 (0.8)	1.0	5 (1.3)	1 (0.4)	0.23
Fever > 38°C	6 (1.5)	1 (0.4)	0.16	35 (9.0)	26 (10.0)	0.66
Severe fatigue	100 (25.6)	72 (27.7)	0.56	220 (56.4)	154 (59.2)	0.47
Arthralgia	4 (1.0)	10 (3.8)	0.01	16 (4.1)	56 (21.5)	< 0.001
Myalgia	23 (5.9)	50 (19.2)	< 0.001	94 (24.1)	128 (49.2)	< 0.001
Axillary lymphadenopathy	1 (0.3)	4 (1.5)	0.08	8 (2.1)	25 (9.6)	< 0.001
Paresthesia	9 (2.3)	4 (1.5)	0.49	18 (4.6)	3 (1.2)	0.01
Headache	18 (4.6)	45 (17.3)	< 0.001	40 (10.3)	127 (48.8)	< 0.001
Uterine contractions	5 (1.3)	N/A	N/A	25 (6.4)	N/A	N/A
Vaginal bleeding	1 (0.3)	N/A	N/A	6 (1.5)	N/A	N/A
Prelabor rupture of membranes	0 (0)	N/A	N/A	3 (0.8)	N/A	N/A

Data are given as *n* (%). N/A, not applicable.

Table 3 Adverse events after the first and second doses of BNT162b2 vaccine in 390 pregnant women, according to the timing of vaccination during pregnancy

	First dose				*Second dose*			
Adverse event	*1st trimester (n = 76)*	*2nd trimester (n = 193)*	*3rd trimester (n = 121)*	P	*1st trimester (n = 52)*	*2nd trimester (n = 154)*	*3rd trimester (n = 184)*	P
Local pain/swelling	73 (96.1)	181 (93.8)	104 (86.0)	0.02	48 (92.3)	140 (90.9)	172 (93.5)	0.68
Rash	0 (0)	2 (1.0)	1 (0.8)	0.68	0 (0)	2 (1.3)	3 (1.6)	0.65
Fever > 38°C	1 (1.3)	4 (2.1)	1 (0.8)	0.67	7 (13.5)	13 (8.4)	15 (8.2)	0.48
Fever ≥ 39°C	0 (0)	0 (0)	0 (0)	N/A	1 (1.9)	2 (1.3)	0 (0)	0.24
Severe fatigue	20 (26.3)	54 (28.0)	26 (21.5)	0.44	35 (67.3)	89 (57.8)	96 (52.2)	0.14
Arthralgia	0 (0)	4 (2.1)	0 (0)	0.13	2 (3.8)	10 (6.5)	4 (2.2)	0.14
Myalgia	5 (6.6)	14 (7.3)	4 (3.3)	0.34	15 (28.8)	38 (24.7)	41 (22.3)	0.61
Axillary lymphadenopathy	0 (0)	0 (0)	1 (0.8)	0.33	3 (5.8)	1 (0.6)	4 (2.2)	0.08
Paresthesia	2 (2.6)	5 (2.6)	2 (1.7)	0.85	3 (5.8)	9 (5.8)	6 (3.3)	0.48
Headache	5 (6.6)	8 (4.1)	5 (4.1)	0.66	2 (3.8)	21 (13.6)	17 (9.2)	0.11
Uterine contractions	0 (0)	2 (1.0)	3 (2.5)	0.29	0 (0)	2 (1.3)	23 (12.5)	< 0.001
Vaginal bleeding	1 (1.3)	0 (0)	0 (0)	0.13	2 (3.8)	2 (1.3)	2 (1.1)	0.34
Prelabor rupture of membranes	0 (0)	0 (0)	0 (0)	N/A	0 (0)	0 (0)	3 (1.6)	0.18

Data are given as *n* (%). N/A, not applicable.

Table 4 Characteristics and blood serology for SARS-CoV-2-specific antibodies in 96 pregnant and 96 non-pregnant women who received two doses of BNT162b2 vaccine

Variable	*Pregnant (n = 96)*	*Non-pregnant (n = 96)*	P
Serum IgG S/CO ratio	27.03 ± 10.72	34.35 ± 10.25	< 0.001
Second dose-to-sampling interval (days)	28.0 (25.25–31.0)	29.0 (27.0–29.0)	0.99
BMI (kg/m^2)	24.45 ± 5.52	25.13 ± 5.37	0.3
Age (years)	32.7 ± 3.7	34.8 ± 4.5	0.001

Data are given as mean ± SD or median (interquartile range). BMI, body mass index; IgG, immunoglobulin G; S/CO ratio, signal-to-cut-off ratio.

Table 5 Obstetric, delivery and neonatal outcomes of 57 pregnant women who received two doses of BNT162b2 vaccine

Outcome	*Value*
Gestational age at birth (weeks)	39.5 (38.7–40.0)
Premature delivery < 37 weeks	0 (0)
Birth weight (g)	3269 ± 410
Miscarriage or IUFD	0 (0)
PIH or pre-eclampsia	1 (1.8)
SGA	3 (5.3)
Gestational diabetes	4 (7.0)
Placental abruption	2 (3.5)
Oligohydramnios	1 (1.8)
Polyhydramnios	2 (3.5)
Induction of labor	17 (29.8)
Vacuum/forceps-assisted delivery	2 (3.5)
Elective Cesarean section	3 (5.3)
Emergency Cesarean section	7 (12.3)
Postpartum hemorrhage	6 (10.5)
Endometritis	1 (1.8)
Neonatal death	0 (0)
Neonatal CPR	0 (0)
Neonatal oxygen support	2 (3.5)
Neonatal invasive ventilation	2 (3.5)
Neonatal fever	0 (0)
NICU hospitalization*	2 (3.5)

Data are given as median (interquartile range), *n* (%) or mean ± SD. *Two neonates were hospitalized in neonatal intensive care unit (NICU) after birth, both due to requirement for invasive ventilation; one of them was diagnosed with respiratory distress syndrome. CPR, cardiopulmonary resuscitation; IUFD, intrauterine fetal demise; PIH, pregnancy-induced hypertension; SGA, small-for-gestational age (birth weight < 10th centile).

age or BMI between pregnant women who were tested and those who were not tested. Pregnant women who were tested were younger than non-pregnant tested controls, but vaccination-to-sampling interval and BMI did not differ between the two groups (Table 4). All serum samples in both the study group and the control group were positive for SARS-CoV-2 IgG. However, pregnant women had significantly lower SARS-CoV-2 IgG serum levels compared to non-pregnant women (S/CO ratio, 27.03 ± 10.72 *vs* 34.35 ± 10.25; $P < 0.001$). Vaccine-induced SARS-CoV-2 IgG levels in maternal serum did not differ according to the trimester of vaccination and were not associated with gestational age on vaccination.

Obstetric, delivery and neonatal outcomes

Of the 390 included pregnant patients, 91 delivered during the study period, of whom 57 completed the second questionnaire regarding obstetric, delivery and neonatal outcomes. All 57 patients received the first dose of vaccine after 26 weeks of gestation at a median gestational age of 32.4 (IQR, 31.2–33.6) weeks. Outcomes are shown in Table 5. Median gestational age at delivery was 39.5 (IQR, 38.7–40.0) weeks, with no cases of preterm birth < 37 weeks. Mean weight at birth was 3269 ± 410 g. None of the pregnancies was complicated by fetal or neonatal death, and two (3.5%) neonates required neonatal intensive care unit admission for respiratory support.

DISCUSSION

In this study, we examined the safety and immunogenicity of the Pfizer/BioNTech BNT162b2 mRNA vaccine in pregnant women. We have shown that there were no additional adverse effects of vaccination in pregnant compared with non-pregnant women. Furthermore, several adverse effects were significantly more common in the non-pregnant control group. Timing of vaccination during pregnancy did not affect the rate or profile of adverse effects.

This study also showed that the BNT162b2 vaccine induced humoral immunity in all vaccinated pregnant women, although SARS-CoV-2 IgG levels were lower in pregnant compared to non-pregnant women. The clinical significance of this difference is unclear, particularly since these levels were still much higher than those reported in patients recovered from COVID-19.

Although this study was not designed to test obstetric outcomes, given that pregnant non-vaccinated women were not included, the results showed that BNT162b2 vaccination in pregnancy is associated with favorable obstetric and neonatal outcomes, comparable to those reported in the general pregnant population. In line with our findings, the Centers for Disease Control and Prevention (CDC) has published recently data indicating that there are no significant differences in adverse reactions to the vaccine in pregnant *vs* non-pregnant women aged 16–54 years[22].

In Pfizer's clinical trial of the BNT162b2 mRNA vaccine, fever occurred in 3.7% of participants after the first dose and in 15.8% after the second dose[12]. Fever in the first trimester of pregnancy is associated with an increased risk for certain types of birth defects, although the absolute risk is small[23]. Our data showing a very low rate of fever following vaccination in pregnant women are reassuring.

Furthermore, the risk for obstetric complications following COVID-19 vaccination seems to be negligible. For example, the rate of vaginal bleeding following

first-trimester administration of the second dose of vaccine was only 3.8%, which is very low when compared to the accepted known rate of 16–27%[24,25]. Similarly, the rates of vaginal bleeding following second- and third-trimester administration of the second dose of vaccine in our study group were 1.3% and 1.1%, respectively, which are much lower than the 2–5% rate reported in the literature[26]. We presume that the increased probability of uterine contractions following the second dose in women who were vaccinated in the third trimester can be attributed to their advanced gestational age. However, uterine contractions following vaccination did not result in any preterm births. Likewise, the CDC has reported a similar incidence of adverse pregnancy outcome in pregnant women vaccinated against COVID-19 compared to pregnant women included in studies that were conducted before the COVID-19 pandemic[22].

We showed that the BNT162b2 vaccine generated humoral immunity among the 96 pregnant women who were tested. While the mean SARS-CoV-2 IgG level was statistically lower in pregnant women than in non-pregnant women following vaccination, the clinical significance of this is yet to be determined. In contrast to our results, Gray *et al.*[18] reported no difference in vaccine-induced antibody titers in 84 pregnant women *vs* 16 non-pregnant women. No differences in antibody titers according to the trimester of vaccination were observed. These findings should be considered with caution since the study was based on two different types of vaccine, and the number of patients included was small. It is unlikely that the difference in antibody levels observed in this study between pregnant and non-pregnant women following vaccination is related to the 2-year age difference between the groups, as Polack *et al.*[12] showed similar vaccine effectiveness across age groups. The decreased vaccine-induced antibody levels in pregnant *vs* non-pregnant women observed in this study may be explained by the relative immunosuppressed state that characterizes pregnant women. Of note, in addition to humoral immunity, the BNT162b2 vaccine induces a cellular immune response, which complements the antibody response but is difficult to quantify. The effect of the vaccine on the cellular immune system may impair the balance between different T-cells, which maintains fetal tolerance and theoretically may lead to adverse pregnancy outcomes such as miscarriage, preterm birth and pre-eclampsia[17]. However, our preliminary data indicate favorable obstetric outcome following vaccination, with similar rates of pregnancy complications to those in the general population. Data regarding mRNA vaccines in pregnant women are limited to 12 pregnant women who were enrolled inadvertently in Pfizer's clinical trial in the vaccine group[12] and small cohort trials published recently[18,22]. Consequently, conflicting statements have been published by public health groups with respect to the need for pregnant women to be vaccinated, creating substantial confusion. Therefore, the data presented in the current study are important and reassuring as they show a low rate of adverse events, including obstetric and neonatal complications, following BNT162b2 mRNA vaccination in pregnant women.

Clinical trials assessing pregnancy outcome and the efficacy of COVID-19 vaccines in pregnant women are urgently needed. It is crucial to determine the advisable timing of vaccination across all three trimesters in order to optimize the balance between the vaccine's efficacy and maternal and fetal safety. Moreover, with the aim of providing evidence-based recommendations, future studies should evaluate maternal–neonatal transfer of SARS-CoV-2 antibodies, as well as long-term infant outcome after administration of COVID-19 vaccine during pregnancy.

This is one of the largest studies to date evaluating COVID-19 vaccine safety and immunogenicity in pregnant women vaccinated with the same type of vaccine. Furthermore, pregnant women were compared to a relatively large and well-matched group of non-pregnant women, and all of the serology blood samples were processed at the same laboratory, preventing data mismatch and bias.

This study is limited by the short time frame, and, consequently, only a small number of participants delivered, restricting our ability to reach firm conclusions regarding obstetric and neonatal outcomes. Second, we did not include a matched control group of pregnant unvaccinated women to demonstrate obstetric outcome related to the vaccine, although the favorable pregnancy outcomes are very reassuring. Moreover, despite the antibody levels indicating humoral immunity, we were unable to assess clinical effectiveness of the vaccine. Another limitation stems from using questionnaires, which could lead to some respondent bias and means that data were missing for the 149 pregnant women who did not complete the questionnaire.

In conclusion, the Pfizer/BioNTech BNT162b2 mRNA COVID-19 vaccine seems to be safe for use in pregnant women at all stages of pregnancy and seems to be highly immunogenic in these women.

REFERENCES

1. World Health Organization. Coronavirus disease (COVID-19) Weekly Epidemiological Update and Weekly Operational Update. https://www.who.int/publications/m/item/weekly-update-on-covid-19---16-october-2020.
2. DeBolt CA, Bianco A, Limaye MA, Silverstein J, Penfield CA, Roman AS, Rosenberg HM, Ferrara L, Lambert C, Khoury R, Bernstein PS, Burd J, Berghella V, Kaplowitz E, Overbey JR, Stone J. Pregnant women with severe or critical coronavirus disease 2019 have increased composite morbidity compared with nonpregnant matched controls. *Am J Obstet Gynecol* 2021; **224**: 510.e1–12.
3. Hantoushzadeh S, Shamshirsaz AA, Aleyasin A, Seferovic MD, Aski SK, Arian SE, Pooransari P, Ghotbizadeh F, Aalipour S, Soleimani Z, Naemi M, Molaei B, Ahangari R, Salehi M, Oskoei AD, Pirozan P, Darkhaneh RF, Laki MG, Farani AK, Atrak S, Miri MM, Kouchek M, Shojaei S, Hadavand F, Keikha F, Hosseini MS, Borna S, Ariana S, Shariat M, Fatemi A, Nouri B, Nekooghadam SM, Aagaard K. Maternal death due to COVID-19. *Am J Obstet Gynecol* 2020; **223**: 109.e1–16.
4. Juan J, Gil MM, Rong Z, Zhang Y, Yang H, Poon LC. Effect of coronavirus disease 2019 (COVID-19) on maternal, perinatal and neonatal outcome: systematic review. *Ultrasound Obstet Gynecol* 2020; **56**: 15–27.
5. Dashraath P, Wong JLJ, Lim MXK, Lim LM, Li S, Biswas A, Choolani M, Mattar C, Su LL. Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. *Am J Obstet Gynecol* 2020; **222**: 521–531.
6. Zambrano LD, Ellington S, Strid P, Galang RR, Oduyebo T, Tong VT, Woodworth KR, Nahabedian JF, Azziz-Baumgartner E, Gilboa SM, Meaney-Delman D, CDC COVID-19 Response Pregnancy and Infant Linked Outcomes Team. Update: Characteristics of Symptomatic Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status — United

States, January 22–October 3, 2020. *MMWR Morb Mortal Wkly Rep* 2020; **69**: 1641–1647.
7. Jering KS, Claggett BL, Cunningham JW, Rosenthal N, Vardeny O, Greene MF, Solomon SD. Clinical Characteristics and Outcomes of Hospitalized Women Giving Birth with and without COVID-19. *JAMA Intern Med* **2020**; 2019: 2019–2022.
8. Allotey J, Stallings E, Bonet M, Yap M, Chatterjee S, Kew T, Debenham L, Llavall AC, Dixit A, Zhou D, Balaji R, Lee SI, Qiu X, Yuan M, Coomar D, Van Wely M, Van Leeuwen E, Kostova E, Kunst H, Khalil A, Tiberi S, Brizuela V, Broutet N, Kara E, Kim CR, Thorson A, Oladapo OT, Mofenson L, Zamora J, Thangaratinam S for PregCOV-19 Living Systematic Review Consortium. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: Living systematic review and meta-analysis. *BMJ* 2020; **370**: m3320.
9. Mullins E, Hudak ML, Banerjee J, Getzlaff T, Townson J, Barnette K, Playle R, Perry A, Bourne T, Lees CC; PAN-COVID investigators and the National Perinatal COVID-19 Registry Study Group. Pregnancy and neonatal outcomes of COVID-19: coreporting of common outcomes from PAN-COVID and AAP-SONPM registries. *Ultrasound Obstet Gynecol* 2021; **57**: 573–581.
10. Martinez-Portilla RJ, Sotiriadis A, Chatzakis C, Torres-Torres J, Espino Y Sosa S, Sandoval-Mandujano K, Castro-Bernabe DA, Medina-Jimenez V, Monarrez-Martin JC, Figueras F, Poon LC. Pregnant women with SARS-CoV-2 infection are at higher risk of death and pneumonia: propensity score matched analysis of a nationwide prospective cohort (COV19Mx). *Ultrasound Obstet Gynecol* 2021; **57**: 224–231.
11. Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, Hernán MA, Lipsitch M, Reis B, Balicer RD. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. *N Engl J Med* 2021; **384**: 1412–1413.
12. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C, Bailey R, Swanson KA, Roychoudhury S, Koury K, Li P, Kalina W V., Cooper D, Frenck RW, Hammitt LL, Türeci Ö, Nell H, Schaefer A, Ünal S, Tresnan DB, Mather S, Dormitzer PR, Şahin U, Jansen KU, Gruber WC. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med* 2020; **383**: 2603–2615.
13. World Health Organization. Background document on the mRNA vaccine BNT162b2 (Pfizer–BioNTech) against COVID-19: background document to the WHO interim recommendations for use of the Pfizer–BioNTech COVID-19 vaccine, BNT162b2, under emergency use listing, 14 January 2021. https://apps.who.int/iris/handle/10665/338671.
14. FDA. Vaccines and Related Biological Products Advisory Committee Meeting, December 17, 2020. FDA Briefing Document Moderna COVID-19 Vaccine. https://www.fda.gov/media/144434/download.
15. Sahin U, Muik A, Derhovanessian E, Vogler I, Kranz LM, Vormehr M, Baum A, Pascal K, Quandt J, Maurus D, Brachtendorf S, Lörks V, Sikorski J, Hilker R, Becker D, Eller AK, Grützner J, Boesler C, Rosenbaum C, Kühnle MC, Luxemburger U, Kemmer-Brück A, Langer D, Bexon M, Bolte S, Karikó K, Palanche T, Fischer B, Schultz A, Shi PY, Fontes-Garfias C, Perez JL, Swanson KA, Loschko J, Scully IL, Cutler M, Kalina W, Kyratsous CA, Cooper D, Dormitzer PR, Jansen KU, Türeci Ö. COVID-19 vaccine BNT162b1 elicits human antibody and TH1 T cell responses. *Nature* 2020; **586**: 594–599.
16. Pardi N, Hogan MJ, Naradikian MS, Parkhouse K, Cain DW, Jones L, Moody MA, Verkerke HP, Myles A, Willis E, LaBranche CC, Montefiori DC, Lobby JL, Saunders KO, Liao HX, Korber BT, Sutherland LL, Scearce RM, Hraber PT, Tombácz I, Muramatsu H, Ni H, Balikov DA, Li C, Mui BL, Tam YK, Krammer F, Karikó K, Polacino P, Eisenlohr LC, Madden TD, Hope MJ, Lewis MG, Lee KK, Hu SL, Hensley SE, Cancro MP, Haynes BF, Weissman D. Nucleoside-modified mRNA vaccines induce potent T follicular helper and germinal center B cell responses. *J Exp Med* 2018; **215**: 1571–1588.
17. Saito S, Nakashima A, Shima T, Ito M. Th1/Th2/Th17 and regulatory T-cell paradigm in pregnancy. *Am J Reprod Immunol* 2010; **63**: 601–610.
18. Gray KJ, Bordt EA, Atyeo C, Deriso E, Akinwunmi B, Young N, Medina Baez A, Shook LL, Cvrk D, James K, De Guzman R, Brigida S, Diouf K, Goldfarb I, Bebell LM, Yonker LM, Fasano A, Rabi SA, Elovitz MA, Alter G, Edlow AG. COVID-19 vaccine response in pregnant and lactating women: a cohort study. *Am J Obstet Gynecol* 2021. DOI:https://doi.org/10.1016/j.ajog.2021.03.023.
19. Beharier O, Plitman Mayo R, Raz T, Nahum Sacks K, Schreiber L, Suissa-Cohen Y, Chen R, Gomez-Tolub R, Hadar E, Gabbay-Benziv R, Jaffe Moshkovich Y, Biron-Shental T, Shechter-Maor G, Farladansky-Gershnabel S, Yitzhak Sela H, Benyamini-Raischer H, D Sela N, Goldman-Wohl D, Shulman Z, Many A, Barr H, Yagel S, Neeman M, Kovo M. Efficient maternal to neonatal transfer of antibodies against SARS-CoV-2 and BNT162b2 mRNA COVID-19 vaccine. *J Clin Invest* 2021; **131**: e150319.
20. Centers for Disease Control and Prevention. COVID-19 Vaccines While Pregnant or Breastfeeding. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/pregnancy.html.
21. American College of Obstetricians and Gynecologists. Practice advisory: COVID-19 Vaccination Considerations for Obstetric–Gynecologic Care, December 2020. https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2020/12/covid-19-vaccination-considerations-for-obstetric-gynecologic-care.
22. Shimabukuro TT, Kim SY, Myers TR, Moro PL, Oduyebo T, Panagiotakopoulos L, Marquez PL, Olson CK, Liu R, Chang KT, Ellington SR, Burkel VK, Smoots AN, Green CJ, Licata C, Zhang BC, Alimchandani M, Mba-Jonas A, Martin SW, Gee JM, Meaney-Delman DM, CDC v-safe COVID-19 Pregnancy Registry Team. Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons. *N Engl J Med*. 2021; **384**: 2273–2282.
23. Graham JM. Update on the gestational effects of maternal hyperthermia. *Birth Defects Res* 2020; **112**: 943–952.
24. Hasan R, Baird DD, Herring AH, Olshan AF, Jonsson Funk ML, Hartmann KE. Association between first-trimester vaginal bleeding and miscarriage. *Obstet Gynecol* 2009; **114**: 860–867.
25. Axelsen SM, Henriksen TB, Hedegaard M, Secher NJ. Characteristics of vaginal bleeding during pregnancy. *Eur J Obstet Gynecol* 1995; **63**: 131–134.
26. Mukherjee S, Bhide A. Antepartum haemorrhage. *Obstet Gynaecol Reprod Med* 2008; **18**: 335–339.

